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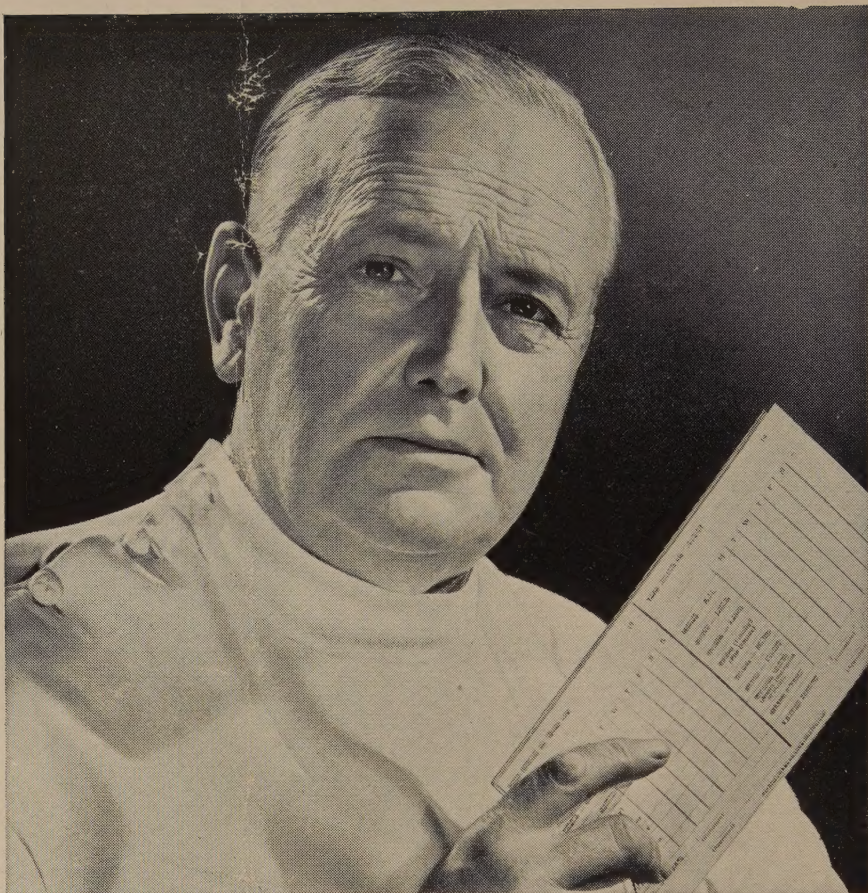
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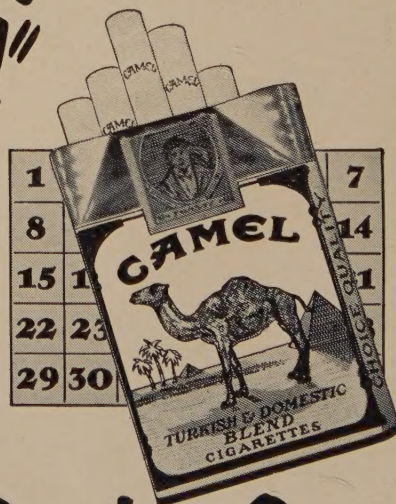
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HYPER-DIETHYLSTILBESTROL THERAPY IN GYNECOLOGY AND OBSTETRICS

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The use of massive doses of the synthetic estrogen, diethylstilbestrol, in the treatment of uterine bleeding during pregnancy was first reported by Karl John Karnaky in 1942 (1). Three years earlier, however, in 1939, a paper appeared by the same author (2) in which large doses of diethylstilbestrol were successfully employed for the first time in the management of functional uterine bleeding. With the publication of these two papers a solid and scientific basis for the management of non-malignant uterine bleeding, in and out of pregnancy, was established for the first time. The medical profession should feel most grateful to Doctor Karnaky for his pioneer work in this field, especially in view of the skepticism and criticism expressed during the "early experimental phase" with massive stilbestrol therapy. Time and numerous clinical studies have well justified Karnaky's confidence in his proposed treatment. So far as the present writer can see, little has been added to Karnaky's original concept by the large number of papers that have been published by numerous physicians, mostly obstetricians and gynecologists. Thus, little can be gained by attempting to summarize these papers or even by giving a bibliography of them. Consequently, they are omitted in this paper, though the writer is certain they can be found, if desired by the reader, in the bibliography of any number of other papers on the subject.

The present writer, at least in this paper, is adding nothing of an original nature to what has already been accepted as good medicine. He will merely report his personal results with high doses of diethylstilbestrol in a group of pathologic obstetric and gynecologic conditions. The writer's experience brings forth this conclusion, that massive diethylstilbestrol dosage is the treatment par excellence of threatened and habitual abortion, premature labor and functional uterine bleeding. Similar therapy is being proved of value in pregnant

diabetic patients, as well as in certain toxemias of pregnancy. However, further study is required in the latter two conditions before complete acceptance is warranted.

The following conditions, with their number of cases, will be discussed: threatened abortion, 12; habitual abortion, 3; premature labor, 12; pregnancy in diabetic patients, 2; toxemia of pregnancy, 3; and functional uterine bleeding, 17. It will be noted that the total number of cases reported adds up to 49. This figure is obviously too small to justify sweeping and definitive conclusions. Nevertheless, the results were so striking with this therapy, that the writer thought it advisable to discuss this relatively small series as a preliminary report. Further studies with larger groups of cases are being collected and, it is hoped, will be reported within the year. Table I gives a summary of the number of cases, the pathologic conditions, the dosage of diethylstilbestrol and the results obtained.

THREATENED ABORTION 12 CASES

The 12 cases of threatened abortion ranged from the sixth to twenty-third week of pregnancy. In each instance there was uterine bleeding—from a few teaspoons to a pretty severe hemorrhage of 300 to 400 c.c. Five cases had uterine contractions, mild to severe, while the remaining seven were free of complainable pain or noticeable contractions. It was felt, from previous experience, that at least three, and possibly four of these cases would have aborted in the normal course of events under treatment formerly prescribed: sedation, rest, morphine, ice-cap, etc. Under diethylstilbestrol, bleeding stopped in all instances but one—in seven cases within three to 12 hours, in two within 24 hours, while the two remaining patients continued to spot for approximately 48 to 72 hours. In view of these latter cases of prolonged bleeding before

cessation, it is felt that therapy should not be too soon discontinued. The five patients with uterine contractions were relieved of their pains within 12 to 18 hours. All patients were kept in bed during active bleeding, in fact until all spotting had stopped—in three cases for three days. Other than diethylstilbestrol and a grain of phenobarbital (or one of the proprietaries) at night, no medication was prescribed.

As stated, one patient continued to bleed and have contractions in spite of therapy, and she went on to the spontaneous expulsion of a two and a half months' fetus. The loss of one pregnancy in 12 threatened abortions gives a successful outcome of 83 per cent.

The treatment instituted, with slight variations in dosage depending upon the severity of symptoms, was as follows: with the onset of bleeding or pain, three tablets,* each of 25.0 mg., a total of 75.0 mg., of diethylstilbestrol, were given at once, followed by one tablet every 15 minutes for 10 doses. Following this, a tablet was given every hour for six doses. The patient was then placed on a daily maintenance dose of four tablets, one every six hours. This was continued up to and including the 36th week of pregnancy. Should symptoms recur—and this happened in one case—the larger dose of three tablets followed by one every 15 minutes is to be repeated.

Four of the 12 patients have delivered fullterm living and normal children; five are at or near term, and two are, at the present writing, in their seventh month. One, as mentioned above, aborted.

Approximately 500 mg. of diethylstilbestrol are given the first day of treatment, followed by 100 mg. per day until the 36th week. Other than one or two patients who complained of nausea, and another who was troubled with more or less persistent vomiting, there were no gastro-intestinal or systemic disturbances of any kind. That pregnant women can tolerate with apparent immunity 1000 times the dosage of diethylstilbestrol as compared with non-pregnant women, was shown in a recent paper by Karnaky (3). Others (4) have given as much as 2,500 mg. daily for two days to a patient in early pregnancy without any local or systemic disturbance. It is thus apparent, and established, that the pregnant woman can sustain an extremely high synthetic-estrogen-titre without any untoward effects.

HABITUAL ABORTION THREE CASES

There were three cases of habitual abortion—each patient had three or more previous spontaneous abortions without apparent cause. One of these women had a fullterm child seven years

previously, only to be followed by the loss of four subsequent pregnancies in their early months.

The three patients were first seen in their fourth, fifth and seventh week of pregnancy respectively. Each was placed on 25.0 mg. of stilbestrol four times a day and continued to the end of the 18th week of pregnancy. Beginning with the 19th week, and somewhat following the routine as suggested in a paper by Smith, Smith and Hurwitz (5), the daily maintenance dose was increased by one-quarter tablet (6.25 mg.) weekly, until the end of the 36th week. The patient seen in her seventh week, who has since delivered, continued to increase, on her own, the quarter tablet weekly to the actual time of delivery at 42 weeks. She was thus taking 225 to 250 mg. daily during the last months. Her estimated total dosage throughout pregnancy was 26,625 mg.! No harm was noted, either in mother or child. Incidentally, as reported by several observers, not a few babies show the hyperestrogenic response by having darkened areolae and linea alba. These pigmented areas soon fade. One other "habitual aborter" has delivered a normal fullterm child. The remaining one is practically at term and is expected to deliver daily.

Excluding two days of spotting in this last patient, none of the three women bled during pregnancy. Though the series is indeed small, the results were 100 per cent successful. It is problematic whether a larger series, particularly with cases showing local or general pathology as the cause of the abortion, would show as great a percentage of success. Future studies will be decisive.

Of all patients that come under the care of the obstetrician, the "habitual aborter," who eventually is given a viable and healthy child, is the most grateful. And, it is as well, a most satisfying feeling for the doctor.

PREMATURE LABOR 12 CASES

There are four patients in whom the bag of waters ruptured three to nine weeks before term. In spite of very large doses of diethylstilbestrol all four patients went on to completion of labor within three to 36 hours following the amniotic rupture. Two of the babies survived. Of the other two, one an anencephalic monster, expired soon after birth; the other from prematurity and atelectasis (32 weeks).

Of the remaining eight patients with threatened premature labor, three exhibited regular uterine contractions; three had vaginal bleeding from a slight amount to the passage of fairly large clots, but without contractions; while the remaining two patients had both uterine contractions and some vaginal bleeding. Placenta previa, abruptio placentae or other known pathology was not established in any of the cases.

The treatment given closely allied that described under Threatened Abortion. Six of the patients carried to term. Two of these were delivered by cesarean section—aged primiparity in one, contracted pelvis in the other. One patient carried for two weeks, the other for four weeks following

*The diethylstilbestrol used in this study was mainly "stils," and in a few cases, "des"—no difference in clinical response was noted between these two products. "Des" (the Grant Process of alpha-alpha-diethyl-4, 4-stilbenediol), a 25.0 mg. tablet, was kindly furnished by the manufacturer, Grant Chemical Company of New York. The 25.0 mg. tablet of "stils" was generously supplied by the manufacturer, Bever Products Company of New York and Miami.

initial therapy. Both had viable fetuses which survived. Excluding the patients with ruptured bag of waters who all soon delivered, six of the remaining eight patients went to term or close to it under the above therapy: a successful "carrying to term" of 75 per cent. Fetal survival in these eight cases was 100 per cent. (Here too, as mentioned under Habitual Abortion, a larger series might or might not show as large a percentage of success.)

DIABETES AND PREGNANCY TWO CASES

Much has been written recently of the relationship between abnormal hormonal balance and toxemia as found in pregnant diabetic patients. The Smiths (6) and White (7) believe that the increase in chorionic gonadotrophin hormone with the concomitant diminution of estrogen and progesterone found in the pregnant diabetic is in large part responsible for the increased percentage of premature labor, stillbirth and neonatal death reported in these patients. By correcting this abnormal hormonal relation, the fetal survival rate was increased 90 per cent in 52 diabetics. This compares with a survival rate of 50 per cent in a group of 38 uncorrected diabetic patients. The intramuscular injection of diethylstilbestrol and progesterone (15.0 mg. of each daily) was employed to bring about a normal hormonal balance. The diabetes was controlled by diet—with insulin where necessary.

The two patients here reported were first seen in their third month of pregnancy. One was a primipara, aged 27 years; the other, 35 years of age, had lost her only other pregnancy three years previously in the fourth month. Both patients were under the care of their physicians—strict dieting and insulin were required in each patient to control the diabetes.

Both patients were placed on four tablets (100 mg.) as a continued daily maintenance dose, with one receiving the additional quarter tablet (6.25 mg.) weekly to the 40th week. No progesterone was used. Both patients delivered uneventfully at term. One baby weighed seven pounds four ounces, the other seven pounds.

Obviously, one can conclude little about two patients. However, from a study of these two cases and those of others, it appears that fairly large doses of diethylstilbestrol might conceivably be an important addition to the treatment of the pregnant diabetic patient.

TOXEMIA OF PREGNANCY THREE CASES

The three patients here reported might be classed in the group of mild pre-eclampsia toxemia. With the exception of one of the patients who showed a mild toxemia in a previous pregnancy, none of the patients gave a history of, or showed signs of, kidney or blood-vascular disturbances prior to the onset of the present pregnancy. They were in their 26th, 29th and 33rd week of pregnancy at the time of the development of the first

toxemic symptoms. In general, the blood pressure readings were not high, ranging from a systolic of 146 to 182 over a diastolic of 72 to 110. Albuminuria was slight to moderate, edema of ankles was present in two patients, and one patient had moderately severe headaches (blood pressure 182-110). Blood chemistry was normal in all three patients.

It has been observed by the Smiths (8) that women with toxemia of late pregnancy have high levels of chorionic gonadotrophin and low levels of estrogen and progesterone in the blood and urine. A similar hormonal imbalance was noted, as mentioned above, in the pregnant diabetic patient. To combat this abnormal relationship of hormones, diethylstilbestrol therapy was instituted. Four tablets (100 mg.) were administered daily to each patient and continued to the time of delivery. Table salt and salty foods were restricted. The diet consisted of roast beef, lean chicken, eggs, fruit and fruit juices, cereals, vegetables both raw and cooked, toast, coffee and tea. The patient was encouraged to drink large quantities of water at all times.

In all three cases, the pressure—though never particularly high—returned to normal within two to three weeks. Albumin and ankle edema completely disappeared in two patients, while the third continued to show small amounts of albumin up to several days following delivery. All patients delivered normal fullterm children. One patient required a cesarean section—indication: primiparity, persistent breech presentation, moderate android pelvis.

FUNCTIONAL UTERINE BLEEDING 17 CASES

Of the 17 patients in this group, six had menorrhagia, seven menometrorrhagia, with the remaining four having irregular periods of marked bleeding alternating with episodes of amenorrhea lasting two to five months. Excluding three cases with small multiple fibromyomata (not truly functional uterine bleeding), and two cases of polypoid endometrial hyperplasia, no gross pelvic pathology was present. As shown previously by the writer (9) (in a group of "functional bleeders" treated with methyl testosterone), endometrial biopsy revealed no apparent relationship between the gross or microscopic endometrial picture and the character or amount of the bleeding. Several patients with marked secretory endometrium had excessive bleeding, as did others with a thin proliferative structural phase of the endometrium. This lack of correlation between the histologic picture and clinical symptoms has been mentioned by not a few writers, notably Hamblen, in his excellent text *Endocrine Gynecology* (10).

Excepting variation in dosage, the treatment given was similar to that described by Karnaky in several of his papers. Irrespective of whether the patient had fibroids or not, three tablets of diethylstilbestrol (75.0 mg.) were given at once, followed by a half-tablet (12.5 mg.) every 15 minutes until the bleeding stopped. (A limit of 10 doses is advisable—almost invariably by this time

the bleeding has stopped completely or is well under control.) One tablet was then prescribed every night for 30 nights. Approximately one-half the patients, essentially the overweight and heavier set women, received in addition thyroid (1-3 gr) daily for 30 days, and one lipoiodine each morning for 60 days. The results in the two groups of cases (stilbestrol with or without thyroid and lipoiodine) appeared similar—the value of the additional therapy being equivocal, at least in this small series.

Menorrhagia in all six patients was immediately checked. Of the seven patients with menometrorrhagia and the four with bleeding associated with amenorrhea, nine stopped bleeding within five to 12 hours after the onset of therapy. There was thus an immediate successful outcome in this group of functional uterine bleeding in 15 out of 17 patients, or 88 per cent. Of the remaining two patients who continued to bleed, one required hysterectomy for fibroids, the other a thorough curettement, which had to be repeated.

The total dosage of diethylstilbestrol varied from 125 to 225 mg. the first day. Other than slight to moderately severe nausea in three patients, controlled readily with antacids, the drug was well tolerated. No untoward side-effects were present.

It is too early at the present writing to describe

more than two to six months of the various patients' subsequent history. Seven of the patients, without further therapy, have had essentially normal menstrual periods during the last two to five months. Three have become pregnant—two for the first time. All the remaining patients showed marked benefit from the treatment—excluding of course, the patient requiring hysterectomy, and the one with repeated curettage. In only one case did the treatment in the original dosage require repetition.

SUMMARY

Diethylstilbestrol, in the form of a 25.0 mg. tablet, has been used in relatively massive doses in the treatment of various obstetric and gynecologic conditions. These include abortions, threatened and habitual, premature labor, diabetes and pregnancy, pregnancy toxemia and functional uterine bleeding.

The highest dosage any individual patient received was 26,625 mg. This was taken by a patient with a history of habitual abortion, over a period of eight months of pregnancy. There were no harmful effects—the delivery was uneventful.

The maintenance of hyper-diethylstilbestroemia in the above-mentioned conditions is associated with a high percentage of successful results.

TABLE I

SUMMARY OF CASES AND DOSAGE OF DIETHYLSTILBESTROL STATED AS TABLETS OF 25.0 MG. EACH

	NO. OF CASES	DOSAGE	SUCCESSFUL RESULTS NO.—PERCENT	PARTIAL RELIEF NO.	FAILURES NO.
<i>Threatened Abortion</i>	12	3 tablets at once, followed by 1 q 15 mins. for 10 doses; 1 q hour for next 6 doses; maintenance daily dose of 4 tablets to 36th week of preg.	11 — 83%	0	1
<i>Habitual Abortion</i>	3	1 tablet 4 times daily to 18th week; then daily dose increased by one-quarter tablet weekly to 36th week. (One patient took 26,625 mg. without ill effect)	3 — 100%	0	0
<i>Premature Labor</i>	12	Similar to dosage under Threatened Abortion	6 — 75% (This excludes 4 patients with ruptured bag of waters)	2	4 (All with bag of waters ruptured at onset of treatment)
<i>Diabetes and Pregnancy</i>	2	One patient: 4 tablets daily maintenance dose to 40th week; Other patient: 4 daily plus one-quarter tablet weekly increase to 40th week	2 — 100%	0	0
<i>Toxemia of Pregnancy</i>	3	4 tablets daily to term (salt restricted, water forced)	3 — 100%	0	0
<i>Functional Uterine Bleeding</i>	17	3 tablets at once, followed by one-half tablet q 15 mins. until bleeding stopped (not more than 10 doses; 1 tablet nightly for 30 nights; overweight patients: in addition to above: thyroid 1-3 grs. for 30 days and 1 lipoiodine tablet each morning for 60 days	15 — 88% (Three patients became pregnant)	0	2 (One had hysterectomy for fibroids; the other: repeat curettage)

ADDENDUM

The basal metabolic rate was determined in 39 of the 49 cases. In 29 patients it ranged from minus five to minus 36 per cent. The remaining 10 cases showed a reading of plus five to plus 20 per cent. The addition of thyroid in the minus patients appeared to be of equivocal value. There were no significant abnormalities in the bleeding or clotting time of any of the patients, neither were there any changes following stilbestrol therapy. Apparently the therapeutic effect of this drug is unrelated to changes in the clotting or bleeding time of the patients. Other than moderate nausea found in three patients in the functional bleeding group, there were no signs of toxicity in the entire series. And in these three cases the toxic symptoms were not of sufficient severity to warrant cessation of therapy.

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ESTROGENS FOR PRE-ECLAMPSIA*

EVAN SHUTE, B.A., M.B., F.R.C.S.C.

London, Canada

Since the Smiths (1), the writer (2), and Muhlbock (3) first demonstrated that the blood of eclamptic women was low in estrogen content, there has been some use of estrogens in the management of the late toxemias of pregnancy (2, 4, 5, 6, 7, 8, 9, 10).

As an illustration of what such treatment has to offer, the following case histories of true pre-eclampsia may be of interest. Those described at length are selected because they illustrate points of some importance in this type of therapy and are chosen from a group of 47 consecutive unselected patients having 50 toxic pregnancies. The other 40 pregnancies are mentioned briefly in the table.

CASE HISTORIES

Case 1. Mrs. S. McK., wife of a physician, a primigravida, aged 35 years. She was first seen when seven months pregnant and was due on November 9, 1942. Her blood pressure on September 6 was 128/86. There was no edema or albuminuria, and she seemed quite normal. On her next visit on October 6, her weight had increased seven pounds, her blood pressure was 156/102, her blood estrogen was negative (11) and there was a faint trace of albumin. Despite the negative estrogen, on clinical grounds she was

given 75 mgm. of synthetic alpha tocopherol acetate per day.

When she returned on October 13th her weight was unchanged, but her blood pressure was 180/114. There was minimal leg edema and plus albuminuria. Her urination had become scanty in the preceding two days. There was no headache, but she occasionally saw spots before her eyes. Accordingly she was given no more Vitamin E, but instead was given five mgm. of stilbestrol per day in order to ward off impending eclampsia.

The next day, October 18, she went into labor spontaneously at 3:00 P. M. with acute tenderness over the lower uterine segment. However, when she went into the hospital just before midnight, October 18, she had already excreted 60 ounces of urine during the day! At 11:00 P. M. her blood pressure was 186/116 and she was seven cm. dilated with a two plus albuminuria. An outlet forceps done at midnight under cyclopropane anesthesia delivered a five pound three ounce normal girl. The placenta came promptly, showing one retroplacental area, about 20 hours old, of firm black clot at one edge. It was six cm. in diameter! She was given 50,000 i.u. of estradiol benzoate intramuscularly three times in the first 24 hours post partum, as well as five mgm. of stilbestrol twice a day for the first three days, until the danger of convulsions had passed.

*From the Shute Foundation for Medical Research.

On October 19 at 9:00 A. M. her blood pressure was 170/122 and she felt well, but she had little or no output of urine. This showed only a trace of albumin, however. On the evening of October 23 her blood pressure was 160/110. She was discharged on October 28 with a blood pressure of 188/90.

On January 4, 1943, her blood pressure was 136/96 and her urine was clear. She has been well since, and has had no further pregnancies.

Case 2. Mrs. O. C., aged 27 years. She had had a miscarriage and then a normal pregnancy. She was due on August 3, 1946.

She had a perfectly normal pregnancy throughout, apart from some neuralgia which responded to thiamin chloride. She was at first given 25 mgm. of synthetic alpha tocopherol acetate daily, and was taking 50 mgm. daily by term. By July 27 she had gained 30 pounds, had a blood pressure of 106/64, showed no edema and had a normal urine.

She went into labor spontaneously on August 4, 1946. Her pains were only moderate, but she was drowsy throughout, as if under morphia. At 8:00 A. M. she delivered a nine pound eleven ounce boy by outlet forceps under cyclopropane anaesthesia. At that time her blood pressure was 136/84 and a catheter urine showed a two plus albuminuria. She was given 100,000 i.u. of estradiol benzoate every four hours for the next 24 hours, then five mgm. of stilboestrol per day for two days. She seemed normal by 5:00 P. M. on the day of delivery and remained so. At 7:00 P. M. her blood pressure was 130/70 and her urine was clear of albumin and remained clear. She has been well since, with another pregnancy almost identical.

Case 3. Mrs. F. S. This woman, aged 31 years, had a premature baby at seven months. This present gestation was due on August 21, 1944. She had a normal pregnancy until July 3, when she spotted blood, but had no uterine pains. At that time she had gained eight pounds during the pregnancy, had a blood pressure of 110/88, no

albuminuria, and only slight swelling of the ankles. Thereafter she was given 30 mgm. of synthetic alpha tocopherol acetate per day until she was seen again on August 1 in the town 60 miles away, where she lived.

On that occasion there was much edema in the face and extremities. There had been oliguria for the preceding two weeks, her urine albumin was two plus, and her blood pressure had risen to 160/108. She was at once taken off vitamin E and instead given four mgm. of stilbestrol per day.

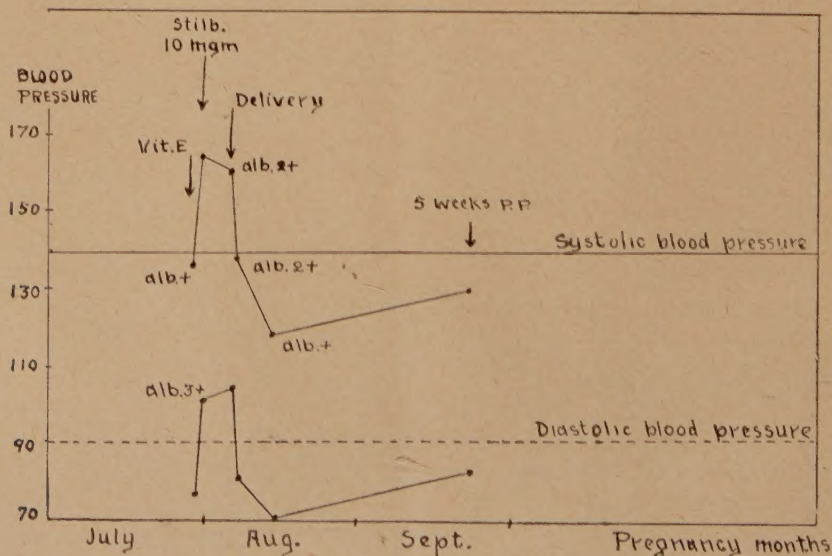
She was brought into hospital in London on August 5 with a blood pressure of 220/128, an albuminuria of 2.0 gm. per cent, only a small urinary output and complaining of steady headache. She was given 50,000 i.u. estradiol benzoate every four hours from August 5 to 7 inclusive, then stilbestrol two mgm. per day. A Voorhees bag was inserted at noon on August 6 when her albuminuria was 3.0 gms. per cent.

After 32 hours of poor pains the bag came out, and an eight pound nine ounce male fetus was delivered at 8:20 P. M. on August 7 by Braxton Hicks version under cyclopropane anaesthesia. It was stillborn. The placenta showed three large white penetrating infarcts. At that time her blood pressure was 190/125 and the albuminuria was 1.0 gm. per cent. At 6:00 P. M. on August 8 her blood pressure was 150/92 and albumin 0.06 gm. per cent.

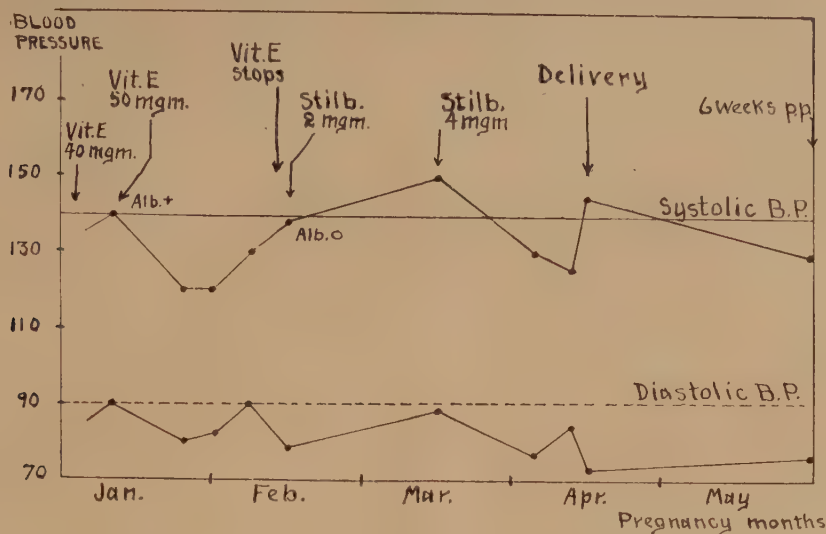
By 9:00 A. M. on August 9 the blood pressure was 150/92 and her albuminuria was less than 0.02 gms. per cent. Her postpartum course was clinically uneventful. On September 16, her blood pressure was 130/94. She has been well since, with no further pregnancies.

Case 4. Mrs. E. S. This woman, aged 29 years, had had a previous pregnancy in 1939 with an eclamptic convulsion during labor.

On June 27, 1942, she was first seen by the writer in consultation. She was due on August 1. At that time she was in the hospital, with great generalized



Case 4.



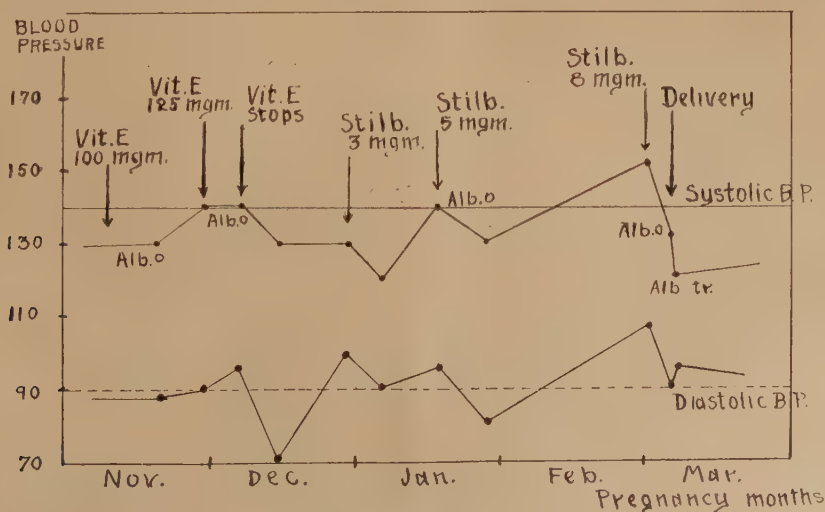
Case 5.

edema, a blood pressure of 136/76, a plus albuminuria, some spots before her eyes, but no liver tenderness or headache. She was at once given 25 mgm. of alpha tocopherol acetate per day, as it was felt that clinically she was not the pre-eclamptic but rather the opposite type of "late toxemia," and that true eclampsia was not apt to repeat. However her blood estrogen proved to be negative! The writer at once warned her physician of this and of the fact that his diagnosis had therefore been reversed, but no heed was taken of the caution.

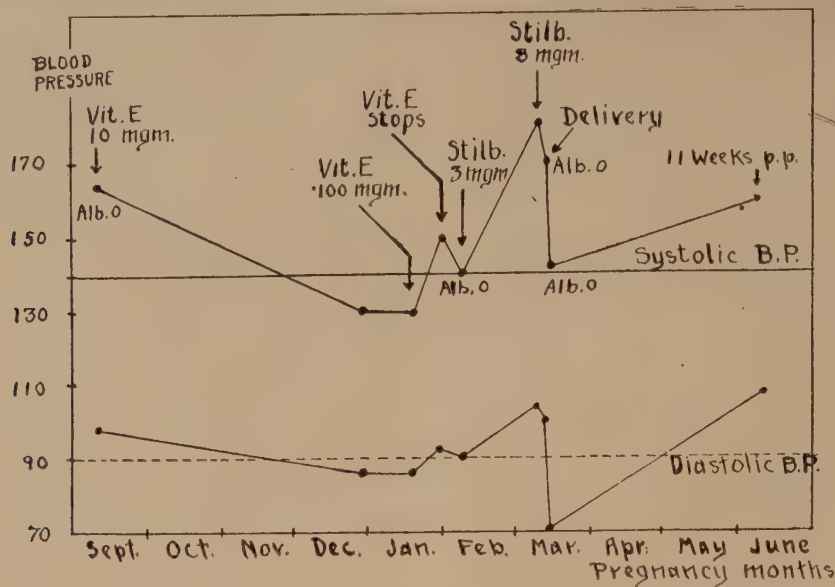
On the night of July 31, she was admitted to Victoria Hospital with extensive, hard, generalized edema, spots before her eyes, no headache nor liver tenderness, but a three plus albuminuria, a small urine output with pyuria, and a blood pressure which had jumped to 164/100. She was given 10 mgm. of stilbestrol per day and was kept in hospital just four days, going home with a one

plus albuminuria, copious urination, no symptoms, and a soft but marked leg edema. She had not been kept in bed while in hospital.

She was delivered spontaneously at 12:30 A. M. on August 6 by her physician after a seven hour labor which had begun spontaneously. Ether was the anesthetic used, and a normal male child of seven pounds eleven ounces was delivered. The blood pressure on this admission was 160/104, and the urine showed a two plus albumin. The placenta was normal. There was some postpartum bleeding and mild shock resulted. For the first two days after delivery she was given five mgm. stilbestrol and 50,000 i.u. estradiol benzoate per day. On August 7 the albuminuria was two plus and the blood pressure 138/80. On August 13 her albumin was down to one plus and the blood pressure was 118/70. She had an almost uneventful puerperium and was sent home on August 15. On September 21 her blood pressure was 130/82.



Case 6



Case 7.

It is of interest that I have since (4 years later) conducted her through the last month of a third pregnancy, this time seeing her first at three weeks from term with a blood pressure of 138/94 and no albuminuria, but with severe edema of the legs. Once again I began with Vitamin E but soon switched to eight mgm. of stilbestrol per day. On this regimen she did very well. Finally she was sectioned and sterilized, making a good recovery. She has been well since.

Case 5. Mrs. G. M. This woman, a primigravida aged 27, was due on April 20, 1946. She ran a normal course until January 10 when she suddenly developed a blood pressure of 140/90. There was minimal edema then, but no albuminuria. She had been taking 40 mgm. per day of alpha tocopherol acetate up to this time. This dose was now increased to 50 mgm. daily. As there was no improvement in four days time, but "blurry vision" developed, this dose was doubled. By January 24 her blood pressure had dropped to 120/80 and there was no edema nor albuminuria. But the pressure rose again subsequently, and on February 12 it was first suspected that she was a true pre-eclamptic. The vitamin E was accordingly stopped. In the next three days her weight decreased one pound and her pressure fell to 138/78, confirming our suspicions. Stilbestrol therapy was cautiously begun, but by March 15 her blood pressure had increased to 150/88. There was still no edema nor albuminuria. The dose of stilbestrol was accordingly raised from two to four mgm. per day. On April 5 the blood pressure was down to 130/76 and a week later it was 126/84.

She began labor spontaneously at 10:00 A. M. on April 15 and at 4:00 P. M. that day a girl weighing eight pounds twelve ounces was delivered under cyclopropane by low forceps. Her blood pressure during labour was 145/72. No special precautions were taken then or in the puerperium, which was uneventful.

At the six weeks postpartum examination her blood pressure was 130/76. She has been well since.

She was delivered again on December 7, 1947, after an uneventful pregnancy, without any toxic manifestations. She took 50 mgm. of alpha tocopherol per day throughout.

Case 6. Mrs. H., a primigravida aged 24 years, was due on March 16, 1946. Her pregnancy was normal from the first, except for a high normal blood pressure—130/88. On 50 mgm. of alpha tocopherol acetate, which was soon raised to 100 mgm. per day, she was taken to November 20 with an unchanged pressure, no edema and no albuminuria. On November 29 her pressure jumped to 140/90 and minimal leg edema appeared. The dose of alpha tocopherol was then raised to 125 mgm. A week later the pressure was 140/96 and she was slightly dizzy. Accordingly pre-eclampsia was suspected and vitamin E therapy was stopped. By December 14, her blood pressure had fallen to 130/70 and there was no edema. There was still no albuminuria, of course.

But on December 29 her blood pressure had climbed to 130/100, with edema, and three mgm. of stilbestrol per day was begun. In five days time the pressure was 120/90 and remained so until January 18 when her blood pressure was 140/96, again without albuminuria. The dose of stilbestrol was then increased to five mgm. per day. Eight days later the blood pressure was 130/80. Different doses of stilbestrol were tried, but on five mgm. per day she reached March 2 with a pressure of 152/108, only moderate leg edema, and no albuminuria. On that day her daily dosage of stilbestrol was increased to eight mgm.

Labor began spontaneously at 4:00 A. M. on March 6. At 4:00 P. M. a breech presented and was extracted readily under cyclopropane anesthesia. A boy weighing six pounds fourteen ounces was obtained. The normal placenta came promptly. At that time her pressure was only 132/90, but as a

precaution she was given three intramuscular injections of 50,000 i.u. estradiol benzoate in the next 36 hours, as well as several oral doses of five mgm. of stilbestrol. At 2:00 P. M. on March 7 her blood pressure was 120/96 and the urine albumin was only a trace. She was discharged in good clinical condition on March 15. At her six weeks postpartum examination the blood pressure was 138/90.

She has had a perfectly normal pregnancy since, taking up to 75 mgm. of alpha tocopherol per day.

Case 7. Mrs. J. H. This woman, aged 36 years, had had two normal pregnancies before. She was due on March 29, 1946. She first came into the office on September 10, 1945, with a blood pressure of 164/98, her uterus being less than three month size, with no albuminuria or edema. On 10 mgm. per day of alpha tocopherol acetate her blood pressure by December 29 was down to 130/86. It began to rise slowly after January 18, 1946, until on 100 mgm. of this vitamin E preparation, it was up to 150/92 on February 1, 1946. She was accordingly taken off tocopherol therapy for a week and her pressure promptly fell to 140/90, still without edema. She was next given gradually increasing doses of stilbestrol until March 5 when her blood pressure reached 180/104, although there was still no edema or albuminuria. She was then given eight mgm. per day until labor began spontaneously on March 13 with a blood pressure of 170/100, no edema or albuminuria. She was given 100,000 i.u. estradiol benzoate at delivery and then half that dose four hours later. Her labor lasted two hours and under cyclopropane anaesthesia she delivered a fine seven pound twelve ounce baby boy spontaneously. The placenta was normal. For the next two days she was given five mgm. of stilbestrol per day. Twelve hours after delivery her blood pressure was 142/70 and the urine was clear of albuminuria. On June 6, 1946, her blood pressure was still 160/108, but there was no albuminuria. There have been no pregnancies since.

Case 8. Mrs. A., a primigravida aged 28 years, had a first pregnancy in 1944-45. In that pregnancy a blood pressure that was 144/100 at 35 weeks was controlled by stilbestrol doses of up to three mgm. per day until labour was induced at 39 weeks with a blood pressure of 132/98, some edema of the face and extremities, but no albuminuria, and a seven pound eleven ounce male infant was delivered. The placenta was normal. On April 2, 1945, her blood pressure was 154/100 but on October 18, 1945, when she was again five months pregnant, it was only 128/84.

In this second pregnancy, due February 23, 1946, she was at first given alpha tocopherol acetate. But by January 31, 1946, she had broken out of control, had a rise in blood pressure at two successive visits from 136/90 to 140/100 and had slight edema of the legs, although no albuminuria. She was at once taken off the tocopherol and given three mgm. per day of stilbestrol. On February 5 her pressure had risen to 166/102, and the stilbestrol was accordingly increased to five mgm. per day. There was still no albuminuria. Three days later the pressure was 164/90 and in another four days, on February 12, it was 130/60, with less

edema. After spontaneous onset of labour she was delivered under cyclopropane anesthesia, after a 12 hours labor, on February 13, 1946, while I was out of town. The female infant weighed seven pounds, thirteen ounces. On admission her blood pressure was 160/98, but no special precautions were taken in labor or her puerperium and she ran a normal postpartum course.

There was no postpartum check on blood pressure or albuminuria, nor has she had another pregnancy.

Case 9. Mrs. L., a primigravida aged 22 years, was due on July 20, 1947. She was normal until July 15 when her blood pressure was only 124/86, but she began to show great edema of the legs and a one plus albuminuria. She had been on alpha tocopherol, but this was now replaced by three mgm. of stilbestrol per day. She subsequently developed severe headaches, but her albumin remained the same. She was accordingly induced on July 23. On admission to hospital her blood pressure was 160/130, and she was given 10,000 i.u. of estradiol benzoate twice before delivery and every four hours afterward for twenty-four hours. Pains lasted six hours, the patient delivering a girl of seven pounds two ounces by mid-forceps at 4:00 P. M. under cyclopropane anesthesia. The placenta was normal. There was great vulvar edema at delivery. At 12:00 noon the albumin had been two plus and the blood pressure 190-130, where it remained all that day. Her vision was never blurred. Her urine showed a three plus albumin until 4:00 P. M. on July 24, when it decreased to a heavy trace. After the first 24 hours of her puerperium she was given 0.25 mgm. ethinyl estradiol orally per day for two days. On July 29 the urine still showed a trace of albumin. On July 31 her platelet count was 225,000. She ran a normal puerperal course and was discharged in eight days as usual. On October 3 her blood pressure was 120/90. She has had no pregnancies since.

Case 10. Mrs. E. K., a primigravida aged 34 years, last menstruated on January 23, 1947. When first seen on March 17 her blood pressure was 132/84 and there was no edema nor albuminuria. On April 28 the blood pressure was 130/80 and there was minimal edema of the ankles. She was taking 10 mgm. of alpha tocopherol acetate daily during this time. By June 13 her pressure had risen to 140/92, but there was no edema nor albuminuria. At that time her dose of tocopherol was raised to 100 mgm. per day. By September 6 her pressure was 138/100, she had gained 23 pounds since her first visit, but there was still no edema nor albuminuria. As it was suspected that she was becoming pre-eclamptic the Vitamin E was stopped for ten days. At the end of that time ethinyl estradiol .05 mgm. per day was given orally. The urine was still clear, there was trivial ankle edema, and the blood pressure was 142/90. On gradually increasing doses of ethinyl estradiol she was taken to October 24 when her blood pressure was 150/106, her weight had increased only 28 pounds over the original weight, her urine showed a very faint trace of albumin, and there was no edema and no headache.

She was induced next day, October 25, had

TABLE I

CASE NUMBER	GESTATION IN WEEKS	WEEKS TOXIC	LB.	CHILD OZ.	SEX	LATER PREGNANCIES	ONSET OF LABOR
11.....	40	3	8	3	m.	?	spontaneous
12.....	40	4	7	15	m.	0	spontaneous
13.....	37	?	6	9	m.	0	cesarean
14.....	40	?	8	10	m.	0	spontaneous
15.....	39	10	6	8	m.	0	induced
16.....	41	3	7	2	m.	0	spontaneous
17.....	37	2	5	10	f.	one normal	spontaneous
18.....	40	3	9	5	m.	0	spontaneous
19.....	41	5	9	—	f.	now pregnant	spontaneous
20.....	43	8	8	14	m.	0	spontaneous
21.....	40	6	6	12	f.	0	spontaneous
22.....	40	3	7	11	f.	0	spontaneous
23.....	38	5	6	11	m.	0	induced
24.....	40	6	8	3	m.	0	induced
25.....	39	9	7	5	f.	0	induced
26.....	35	?	4	—	m.	3	induced
27.....	42	1	8	7	m.	0	induced
28.....	39	1	7	12	m.	0	induced
29.....	39	6	7	7	f.	0	induced
30.....	37	24	7	3	f.	0	spontaneous
31.....	40½	1	5	10	f.	0	induced
32.....	36	1	6	10	m.	one normal	spontaneous
33.....	43	5	7	6	f.	one normal	induced
34.....	40	1	10	3	m.	0	induced
35.....	37	?	6	9	m.	0	cesarean
36.....	41½	2	8	3	f.	0	induced
37.....	40½	½	8	—	m.	0	induced
38.....	36	8	4	15	f.	0	spontaneous
39.....	39	2	7	15	m.	0	spontaneous
40.....	39	1	6	1	m.	0	spontaneous
			6	7	f.		
41.....	39	12	6	15	m.	0	induced
42.....	41	12	7	7	m.	spont. abort.	spontaneous
43.....	35½	6	5	8	f.	0	spontaneous
44.....	40½	5	6	3	m.	0	spontaneous
45.....	37	3	6	13	m.	one normal	induced
46.....	32	5	3	5	m.	0	spontaneous
47.....	33	8	4	9	f.	0	cesarean

moderate pains for five hours, and delivery occurred under cyclopropane anesthesia, a girl weighing seven pounds 13 ounces coming by easy mid-forceps. At delivery her blood pressure was 180/120. The placenta was negative. There was mild postpartum shock for four hours, and her liver was tender for at least six hours. During her induction and for twenty-four hours afterward she was given 100,000 i.u. estradiol benzoate intramuscularly every four hours. After that she received 0.25 mgm. of ethinyl estradiol per day for two days. Her blood pressure on October 26 on two readings was 152/118 and 140/120 and her urine was clear of albumin. On October 27 there was a two plus albumin. Late on October 29 she suddenly showed in the late evening a blood pressure of 190/120 and a two plus albuminuria. Accordingly she was given 200 mgm. of alpha tocopherol per day. Next day her albumin had fallen to one plus and her blood pressures ranged from 170/130 to 150/120. On November 1 her urine was free of albumin and her blood pressure was 156-108. She ran an otherwise normal puerperal course and was discharged on November 4 with a blood pressure of 140/100. On December 9, her blood pressure was 136/72 and she seemed normal.

DISCUSSION

Case 1 (like Cases 33, 45, 47) illustrates why we have been apprehensive of administering a daily dose of stilbestrol larger than eight mgm. to a pregnant woman near term. We suspect that big doses of estrogens can induce abruptio placentae in

such a woman, if toxic (8). That thrombocytopenic purpura may be so induced is also a possibility whether in the mother (8, 12) or in the fetus (Case 33). Kellogg (13) expresses the fear that massive doses of stilbestrol given to these women may increase water retention. However, the truth of the matter should soon be much clearer, as in many centres at the moment much larger doses of estrogens than we have dared to use are being given to women throughout pregnancy until term, based upon the interesting and valuable work of Karnaky (14).

It is idle to claim that eclampsia should always be foreseeable clinically and that suitable antenatal precautions, apart from early induction of labor, can regularly ward it off. For example, consider Case 2. In the future it is to be hoped that laboratory tests will be evolved which will be able to give the alarm in time, but such pertinent and practicable laboratory methods are still to be sought. When found they must be widely used, as clinical differential and diagnostic criteria will probably still remain inadequate.

We have long believed that vitamin E could precipitate eclampsia in a true pre-eclamptic (15). Further evidence to support that view appears in many of our records, but in those quoted in this paper we might point to the data in Cases 1, 3, 4, 5, 6, 7. All of our pregnant patients receive alpha tocopherol in doses of 10 to 150 mgm. per day from the first antenatal visit. This often controls uterine bleeding or pains (16, 17) at any stage of pregnancy, but the use of tocopherols must be

carefully scrutinized at or near term for the reasons given.

It is to be noted that in this series of 50 toxic pregnancies fully 60 per cent went to 39 weeks or more, that the average duration of all was 36½ weeks, that only 46 per cent were finally induced or sectioned, and that the average birth weight of the boys delivered was seven pounds eight ounces and of the girls six pounds 14 ounces. Moreover, fully 96 per cent of the 50 toxemic pregnancies produced live infants and only six per cent weighed 2500 gms. or less, including one set of twins.

When the birth weight of these infants is compared to that reported for our large series of late toxemias of the opposite type (18) it will be seen that the fetal prospects of the latter were somewhat brighter, but that both sets of newborn weighed more than could have been anticipated under any other rationale of toxemia management.

What was also striking was the rapid subsidence after delivery of any hypertension, edema and albuminuria in most of these toxic women, and the fact that of the few who have had later pregnancies enduring five months or more only four were toxic. (Cases 2, 4, 8 and 46 above.)

The late onset of albuminuria in these cases is perhaps significant.

The recent theory of the Smiths (8) that the "enzyme" responsible for eclamptic toxemia is proteolytic jibes well with the writer's observation of 13 years ago that estrogens were antiproteolytic (19) and for this and other reasons were indicated in the therapy of eclampsia.

In the same symposium under the editorship of Foster Kellogg (8) Hertig comments on the remarkable fact that in eclamptics coming to autopsy there is a thickened glomerular basement membrane but that this is not found in fatal cases of "pre-eclampsia." Would it not be logical to attribute this fundamental difference to the fact that the two "toxemias" usually so described are two different entities, most of the so-called pre-eclampsia cases really belonging to a very different type of toxemia? This idea of two principal clinical types of late toxemia has much other evidence to recommend it, of course, as we will discuss in a later paper, and is the basis of the standard classification of the Committee on Maternal Welfare. But in the majority of papers on the subject of late toxemias obstetricians still continue to lump both types together for identical treatment. I believe that such a view is irrational, and one of the great misconceptions to be blotted out of our minds before the management of the toxemias can be improved.

All of the patients cited in this paper were ambulant throughout!

Prophylaxis must always be the basic aim of anyone interested in the management of pregnancy toxemia. Treatment of the condition once it has become firmly established always entails the occasional tragedy and some degree of temporary or permanent impairment of the health of the mother, at least. The most stimulating and valuable suggestion toward prophylaxis that has come to the writer's notice is Kellogg's (13) idea that ante-conceptional treatment of the sperms of the

sire can perhaps produce a stronger conceptus, better nidation, and hence a more normal gestation. It is to be hoped that this line of thought will be pursued by other workers in this field. It had occurred to the writer, and he now has a prospective sire on vitamin E (20) therapy with the possibility in view of avoiding a recurrent toxemia.

Could it be that the beneficial effect of estrogens on blood pressure in many of our cases was due to an inhibitory influence on the pressor factor of the anterior pituitary just described by Hase (21)?

It may be apropos to conclude with a word on the writer's theory of the "late toxemias" as a group, drawing an analogy from diabetes mellitus, (15) another endocrine upset. In that condition, too much insulin leads to hypoglycemic coma or convulsions, too little to hyperglycemic coma. The two types of coma are superficially similar, but a rough therapeutic differentiation may be made by giving glucose to the stuporous patient, since aggravation of the hyperglycemic type is not as dangerous as the worsening of hypoglycemia. Each type can be modified toward the other, although the conditions lie at opposite poles of an endocrine axis. Perhaps late toxemias of pregnancy are somewhat analogous. At one pole of an estrogen axis stands the common high estrogen type, tending to terminate in abruptio placentae and fetal death. At the other pole lies true eclampsia tending to convulsions. The patient can be moved along that axis, we suspect, by giving the first type too much vitamin E and the second one too much estrogen. This will be illustrated, perhaps, by a scrutiny of the accompanying graphs. Clinically, the patients at the poles are often roughly similar in gross appearance. But a safe and relatively quick differential is the response to estrogen administration. It is much safer to trifle with the high estrogen than the low estrogen type.

Obviously this analogy has its weakness, but it may tend to make our views more comprehensible and further study will indicate how much truth there is in it.

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TOCOPHEROL LEVELS AND THEIR DETERMINATION IN BLOOD PLASMA

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The treatment of muscular dystrophies with Vitamin E† was reported by Stone (1) and Bicknell (2). The treatment with tocopherol of patients with amyotrophic lateral sclerosis, and the spectacular results attained in other neuromuscular disorders reported by Wechsler (3), led to the treatment of primary fibrositis with Vitamin E or tocopherol by Steinberg (4) with excellent results. Apparently, no attempts were made to determine quantitatively the tocopherol values in blood, nor to correlate tocopherol values in blood at the onset of the disorder, during treatment with Vitamin E, nor upon recovery.

The object of this investigation was to determine if such a correlation exists. To that end, there were obtained (1) base values, (2) values during treatment (a) orally, and (b) topically, and (3) values after recovery. An attempt was made to determine if increase of blood plasma tocopherol levels (bptl) coincided with decrease of intensity of inflammatory reaction.

EXPERIMENTAL

For the chemical estimation of blood plasma tocopherols, the hydrogenation method of Quaife and Harris (5) with the simplified hydrogenation technique of Quaife and Biehler (6) was used. The tocopherol determination was made with the Emmerie-Engel reagents (7), ferric chloride and a, a'-dipyridyl. The apparatus used for the photometric measurements was a Coleman universal spectrophotometer. All determinations were performed at a wave length of 520 Mu. Synthetic a-tocopherol (Merck) was employed as a standard for plotting the spectral transmittance curve (Fig. 1). This was plotted using 60 micrograms, a-tocopherol in 10 ml. absolute alcohol in which all the reagents were dissolved. The spectral region selected was 520 Mu,

$$E \frac{1 \text{ per cent}}{1 \text{ cm.}} \text{ equals } 410$$

as it permitted a sensitive working range for five

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†The terms *Vitamin E*, *wheat germ oil*, *tocopherols*, unless specifically denoted, are interchangeably employed.

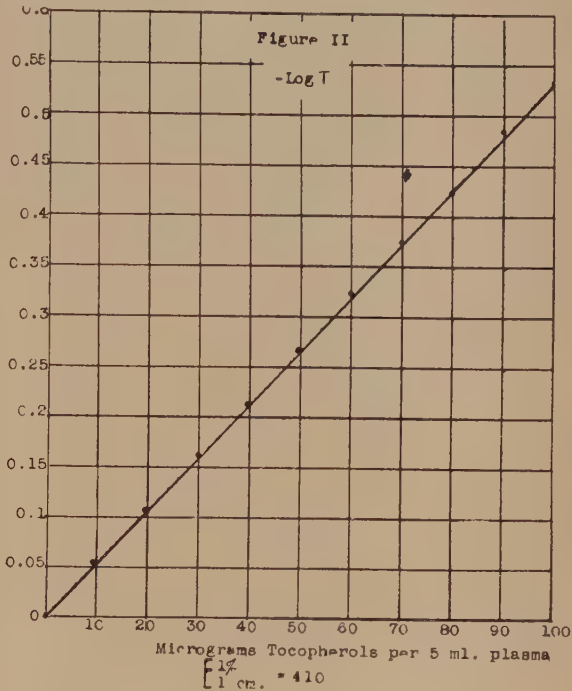
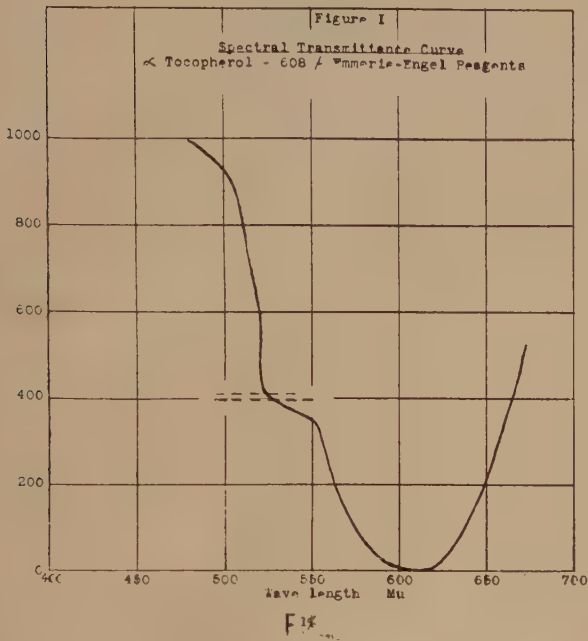
ml. of blood plasma as shown in the concentration curve (Fig. 2) and gave the desired precision.

The formula of Quaife and Harris (5) was used to calculate the determinations in milligrams/per cent tocopherol. As five ml. plasma was used in each determination, their formula was reduced to the simplified expression: 30 x mg. tocopherol in five ml. plasma equals mg. per cent tocopherols.

Twelve different samples of plasma from as many supposedly non-Vitamin E deficient patients were used as normals. By the method employed, an average of 1.19 mg./per cent tocopherol was found. The bptl in normal individuals varied from 0.94 to 1.28 mg./per cent, 1.19 mg./per cent being the average (see Table 1). This is in agreement with a group of normals reported by Quaife and Harris (5) and Darby, et al (8). The former reported a range of 0.9 to 1.6 mg./per cent, with the mean value of 1.2 mg./per cent. The latter reports a mean value for ten normal adults as 1.06 plus or minus 0.06 mg./per cent.

The blood plasma of each of four patients with the clinical diagnosis of fibrositis due to Vitamin E deficiency was assayed for bptl before treatment. By the method employed, an average of 0.72 mg./per cent (39.5 per cent lower) was found, with a high of 0.83 mg./per cent (30.3 per cent lower), and a low of 0.63 mg./per cent (47 per cent lower). The consistency of the correlation in this group was apparent, in that the lowest bptl was found in an advanced case of fibrositis, and the highest bptl (although lower than the normal range) was found in a mild case of fibrositis (see Table II). One patient was treated with local external applications of wheat-germ oil. Two patients were given the same external treatment, but in addition had oral administration of 100 mg. a-tocopherol acetate per day. One patient had oral administration of 100 mg. a-tocopherol acetate per day without any external applications of wheat germ oil. Redeterminations of bptl were performed after two weeks duration of treatment. An average rise of 0.56 mg./per cent bptl was found, with a high rise of 0.71 mg./per cent and a low rise of 0.31 mg./per cent.

The wheat-germ oil used was found to have a concentration of 2.67 mg. a-tocopherol per gram of oil and was incorporated into an absorbable ointment base. The method of Kaunitz and Beaver (9) was used for determination of tocopherol in the oil and the value found was in good



agreement with the tocopherol content of germ oil by Hove and Hove¹⁰) who reported values of 2.74 mg. per gram of oil.

DISCUSSION

By the material and method given above, a consistent correlation seems to exist, between the bptl and ingestion or inunction of tocopherols or Vitamin E. There was also observed an inverse relation between the rise of bptl and symptoms of vitamin E deficiency as exhibited in fibrositis. In view of the fact that Fe has a destructive effect upon vitamin E (a fact upon which work with vitamin E-free diets is based), it would appear that lessening of ingestion of Fe during treatment with vitamin

E is indicated: this phase of the subject will be published later.

SUMMARY AND CONCLUSIONS

- 1. The hydrogenation method for the determination of bptl by the aid of the Coleman spectrophotometer is discussed.
- 2. An inverse relation between bptl and symptoms of vitamin E deficiency as exhibited in fibrositis was observed.
- 3. Increase of bptl either by ingestion of α -tocopherol acetate, or by inunction of vitamin E containing wheat germ oil was found. This increase of bptl was found to coincide with the mitigation of symptoms of fibrositis.

TABLE I

RANGE OF BLOOD PLASMA TOCOPHEROL LEVELS IN NORMAL ADULTS			
SUBJECT	AGE	SEX	MG. PER CENT TOCOPHEROLS
1	57	M	1.21
2	56	F	1.28
3	31	M	0.94
4	35	F	0.96
5	39	F	1.26
6	36	M	0.96
7	37	F	1.20
8	48	M	1.17
9	22	F	1.11
10	80	M	0.96
11	50	M	1.16
12	80	M	1.14
Average normal tocopherol level 1.19			

TABLE II

RANGES OF BLOOD PLASMA TOCOPHEROLS IN CASES OF FIBROSITIS						
CASE	AGE	SEX	MG. % TOCOPH- EROLS BEFORE TREATMENT	DEVIATION FROM NORMAL MG. PER CENT	MG. % TOCOPH- EROLS AFTER TREATMENT	RISE IN 14 DAYS MG. PER CENT
1.....	60	F	0.74	0.45	1.30	0.56
2.....	58	M	0.67	0.52	1.38	0.71
3.....	24	F	0.63	0.56	1.30	0.67
4.....	40	F	0.83	0.36	1.14	0.31

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A NEW APPROACH TO THE CONTROL OF ATHEROSCLEROSIS

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The availability of preventive and therapeutic measures for the effective control of atherosclerosis assumes rapidly increasing importance in view of the rising death rate from this disease among middle-aged adults. The extensive experimental and clinical studies of Dauber and Katz, Duff, Bruger, Hueper, Pollack, Steiner and Kendall, Kountz and many others (1-14) have contributed a great deal to the elucidation of the causation and causative mechanism of this disease, and have supplied valuable information as to its possible preventive and therapeutic management in man.

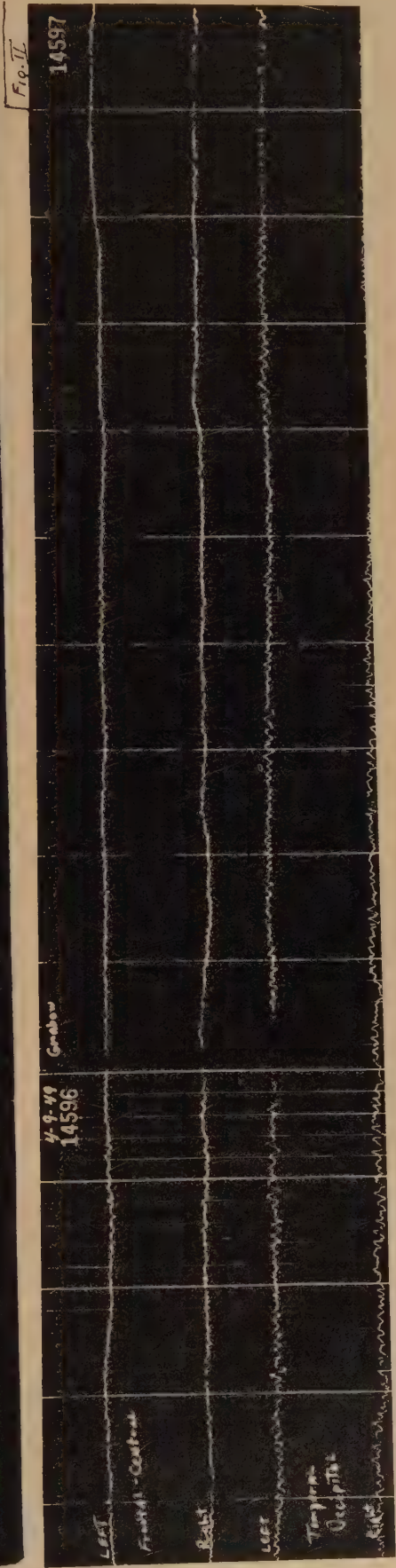
The concepts developed by Hueper appear to be particularly significant in this respect since they provide not only the most plausible explanation of the causal factors involved in the development of the atheromatous arterial lesions, but open a rational and apparently effective way for their prevention and therapy. Hueper in his anoxemia theory of arteriosclerosis states that the interference with the oxygenation and nutrition of the arterial walls, with the resulting decreased vitality of the endothelial lining and reactive endothelial proliferation and foam cell formation, is caused by

the precipitation of cholesterol from the plasma on the endothelial cells. The precipitation of the plasma cholesterol, in turn, is the result of a colloidal plasmatic disturbance affecting the dispersion of the lipoids and lipids which may be produced either by an excessive increase of cholesterol in the plasma or by an abnormally low content of its colloidal stabilizers, such as albumin and lecithin.

Clinical and experimental evidence indicates that disturbances of the oxygen and fat metabolism are related to persistent or transitory increased lability of the plasma lipoids and their tendency to form coarser colloidal floccules. It appears logical, therefore, to institute for the prevention and therapy of atherosclerosis, those measures which decrease the incidence and degree of dietary hypercholesterolemic or hyperlipemic episodes, stimulate the oxidative metabolism, mobilize cholesterol from tissue depots, and stabilize the colloidal equilibrium of the plasma lipoids.

For accomplishing the effects outlined, patients with subjective and objective symptoms of atherosclerosis have been treated during the past few years with a vitamin-hormone combination which, to judge by the results obtained on several thousand

*Authors wish to thank "Vascular Research Foundation" for supplying Oxytropin and Lipotropin used in this investigation.



patients,* seems to represent a promising approach to an effective control of this disease. The particular type of therapy developed and used during this period appears to be equally effective in local (coronary, cerebral) as well as generalized atherosclerosis and proves to be of definite benefit in diabetic atherosclerotic complications.

All patients exhibiting symptoms of atherosclerosis are placed on a diet high in protein and low in fat, especially animal fat. Advanced cases are given three times daily with meals 10 tablets, each containing 422 mg. of choline dihydrogen citrate, 134 mg. of inositol, and two mg. of pyridoxin hydrochloride, i.e., the lipotropic factors of the vitamin B complex. In addition to this medication they receive three times daily a tablet containing the oxytropic factors of the B-complex (thiamin chloride 20 mg., riboflavin 10 mg., niacinamide 120 mg.), 100 mg. of ascorbic acid, and thyroid extract in amounts varying from six mg. to 60 mg. The dose of thyroid extract given is kept low at the start of the treatment, since it was found clinically that the accentuation of the oxidative metabolism must be done gradually so as to avoid symptoms of intolerance. A rather low dose level of thyroid extract is maintained also in patients between 70 and 90 years of age (minimum six mg., maximum 15 mg.). The dose of thyroid in the oxytropic vitamin tablet is increased to the next higher dose in weekly intervals, the maximal dose in most instances does not surpass 30 mg. (The maintenance dose of thyroid in the cases which follow was 20 mg. tid.).

A beneficial effect of this treatment was evident subjectively and objectively in the great majority of patients and was in some cases quite spectacular. The symptomatic improvement was noticeable in most instances within a few weeks after the start of the vitamin-hormone therapy, but occasionally several months elapsed before definite signs of a therapeutic effect became apparent.

The following histories of four advanced cases of atherosclerosis are presented for demonstrating the effectiveness of the treatment proposed in different types of atherosclerosis.

CASE 1

Cerebral Arteriosclerosis

A. G., age 58, white, male. His memory started to fail in January, 1947. Following a fall and injury to his head one year later, loss of memory was more progressive and became complicated by dizzy spells and headaches. His personality started to change. Formerly an alert and keen businessman, he became dull, apathetic, with slow gait and without recollection of any events of the last twenty years of his life. At a neurologic examination in a leading New York hospital, a pneumoencephalogram showed generalized symmetrical dilatation of the lateral ventricles and an electroencephalogram exhibited some disorganization of the normal rhythms bilaterally and bursts

*Five thousand three hundred and seventy treated with oxytropic factors alone since 1945.

One thousand eight hundred and forty-six treated with oxytropic and lipotropic factors combined since August, 1947.

of low voltage delta waves over the left occipito-temporal region (Fig. 1). Final diagnosis on that occasion was generalized and cerebral arteriosclerosis.

When first seen at the Institute of Vascular Medicine in July, 1948, A. G. appeared to be apathetic, disoriented, dull and without memory of recent events. The physical examinations gave the following findings: Moderate sclerosis of the retinal vessels, heart not enlarged, BP 150/80, regular sinus rhythm, no edema and no clubbing of extremities; laboratory findings: Hb 86 per cent, leukocytes 8,600, 76 per cent polymorphonuclear leukocytes, urine without abnormalities, blood plasma cholesterol 196 mg. per 100 cc., cholesterol esters 153 mg. per cent; ECG: left ventricular strain (depressed ST¹ and ², elevated ST³, left axis deviation); X-ray plate of chest: calcific plaques, aortic knob; abdomen: calcified pelvic vessels. GI X-ray series: normal.

The patient was placed immediately on the hormone-vitamin therapy; (during the first month, he had to be housed in an institution because of his mental condition). After four months his memory started to return and after six months his memory power was practically restored to normal, he had become again alert and oriented, and was able, since spring 1949, to engage again in business activities. An encephalogram taken in April, 1949, was normal (Fig. 2). During the observation period, the plasma cholesterol content dropped to 151 mg. per cent and the cholesterol ester content to 105 mg. per cent four months after the start of the treatment; these values reached their lowest point at six months (138 mg. per cent and 119 mg. per cent) and have risen since that time to pre-treatment levels.

CASE 2

Coronary Atherosclerosis

J. R., age 46, white, male. No previous illness. The chief complaint had its onset six years ago—attacks of substernal oppression with pains radiating to left arm. Medical examination at that time revealed posterior wall infarct. Precordial pain continued to occur on effort and after eating, and was relieved by rest and nitroglycerin. For the past year no relief was obtained from nitroglycerin; narcotic medication given three times daily had to be resorted to.

J. R. was first seen in November, 1948. His heart at that time was of normal size, there were no murmurs and no thrills. ECG revealed a Q₂-Q₃ pattern characteristic of an old posterior wall infarct. BP 120/70. X-ray examination revealed a normal cardiac silhouette with calcified plaques in the aorta, also calcifications of the pelvic and leg arteries. Laboratory findings: Erythrocytes 5.8 millions, leukocytes 11,000, 63 per cent polys. Plasma cholesterol: 486 mg. per cent, cholesterol esters 384 mg. per cent.

The hormone-vitamin therapy was given. The patient lost all anginal symptoms after four weeks and has remained symptom-free since. This symptomatic improvement was accompanied by marked decreases in the plasma cholesterol and cholesterol

TABLE II

DATE	11/16/48	11/27/48	12/6/48	12/11/48	1/8/49	2/5/49	3/5/49
Total Chol.....	486	432	309	277	163	269	255 Mg. %
Ester Chol.....	384	334	240	180	93	180	167 Mg. %

ester levels during the first two months of the treatment followed by a gradual rise of both values since that time (Table II).

Case 2 was chosen from the group of coronary atherosclerotics—under therapy with both oxytropic and lipotropic factors—because of the wide range of his cholesterol readings. Most of the other cases of coronary disease show equally good symptomatic improvement. A small number, however, do not get complete freedom from anginal pain even after as long as a year of therapy. The continuation of therapy seems justified, however, in view of their local and general symptomatic improvement and for the purpose of stabilizing the colloidal equilibrium of the plasma lipoids for prevention or retardation of the atherosclerotic process. More time will be necessary to observe whether prolonged therapy will finally result in complete freedom from anginal pain in the few refractory cases.

CASE 3

Generalized Arteriosclerosis with Hepatomegaly

C. H., age 69, white, male, no serious previous illness except for cholecystectomy at age 61. When first seen in October, 1948, he complained of fatigue with occasional dizzy spells and dyspnea which had been getting worse progressively over a period of a year. A severe attack, during the past summer while vacationing in Canada, was considered to be the result of his cerebral arteriosclerosis. Physical examination revealed moderately sclerotic retinal vessels, normal heart, BP 160/70, liver edge at the level of the umbilicus. Laboratory findings: Hemoglobin 82 per cent, leukocytes, 10,800 with 72 per cent polymorphonuclear cells, erythrocytes 6,000,000; urine: albumin one plus, glucose negative. X-ray examination showed sclerotic thoracic aorta, calcifications of leg arteries and abdominal aorta. Gastrointestinal X-ray examination was negative except for diverticulosis of the large intestine. Intravenous pyelogram gave a negative result. ECG was within normal limits. Bromsulphthalein liver function test revealed 60 per cent dye retention. Icteric index was 26 units and cephalin flocculation test was two plus. Plasma cholesterol was 304 mg. per cent and cholesterol esters 232 mg. per cent.

Six months after having been on the hormone-vitamin therapy, the subjective symptoms had disappeared, BP 120/80, the liver was of normal size, the icteric index had dropped to nine units, the Bromsulphthalein test showed only 12 per cent dye retention and the cephalin flocculation test was negative. The plasma cholesterol level dropped after seven weeks to 142 mg. per cent and that of cholesterol esters to 61 mg. per cent. Subjectively,

the patient felt completely well and had resumed his full duties.

Case 3 was selected to illustrate again the combined local and general therapeutic effect—beneficial despite the failure to make a pre-treatment etiological diagnosis of the severe liver disease.

CASE 4

Atherosclerotic Gangrene of the Leg with Diabetes Mellitus

J. D., age 69, white, male, had no history of previous serious illness, sought medical advice in January, 1949, because of pain and swelling of the left foot. These conditions had been present for several weeks and had led to a blackish discoloration of the third and fourth toes. Before coming to the Institute of Vascular Medicine, he had been advised to undergo a mid-thigh amputation of his leg. Since he was found to be diabetic, he was taking protamin zinc insulin daily and observed a moderately restricted diet.

The physical examination showed moderately sclerotic retinal vessels, heart was not enlarged, BP 110/78, bilaterally, abdomen and prostate normal; Dorsali pedis and posterior tibialis as well as popliteal arteries of both legs were without palpable pulsation. Pulsations could be felt in the femoral arteries. A loud bruit was heard over each femoral artery in the inguinal region. Oscillographic readings at both feet and ankles revealed no oscillations. The middle toe and the half of the fourth left toe were black. The left foot was moderately swollen, red and tender. Laboratory findings: Hemoglobin 90 per cent, leukocytes 10,000 with 75 per cent polymorphonuclear cells, plasma cholesterol 255 mg. per cent, cholesterol esters 137 mg. per cent, blood glucose 240 mg. per cent; Urine: glucose two plus, no albumin. ECG showed a Q^2-Q^3 pattern characteristic of old posterior wall infarction. X-ray examination showed a normal cardiac silhouette with a sclerotic aorta, and calcifications of the arteries of the legs. The gall bladder was roentgenologically normal.

The patient was placed on the hormone-vitamin therapy; protamin zinc insulin therapy (15 units) daily was continued. Procain penicillin, 300,000 units, was given intramuscularly, three times a week and a mild antiseptic ointment was used in dressing the diseased toes. No restrictions on his activity except those imposed by pain in the foot were ordered, since the treatment was ambulatory. After two weeks, the swelling, redness and tenderness of the foot started to subside. After four weeks, signs of demarcation of the gangrenous areas appeared. The gangrenous portion of the fourth toe sloughed off after eight weeks and that of the third toe after 10 weeks. Two weeks later the wounds were healed and dry. During this

period of treatment the urine became sugar-free and the insulin was gradually reduced to 10 units daily. Blood sugar level stood then at 119 mg. per cent; glucose tolerance test which at the start of treatment showed 240 mg. per cent, 362 mg. per cent and 394 mg. per cent, became after three months 119 mg. per cent, 214 mg. per cent, and 269 mg. per cent. The plasma cholesterol content was 138 mg. per cent, against 255 mg. per cent at the start. Although no posterior tibialis arterial pulsation could be detected (in either leg), the popliteal pulsation could now be felt. Patient returned to work three months after start of therapy, fully ambulatory, with previously gangrenous leg now exhibiting a nearly normal color and temperature.

There was no doubt in the minds of the clinicians who saw his leg at the outset of therapy, that this patient's gangrene was the result of atherosclerosis primarily, (not infection), and that a mid-thigh amputation would soon be indicated. It is felt that permitting the patient to be ambulatory (thereby aiding the hemodynamics of the vascular system) while using the therapeutic regimen outlined above, would seem to simplify to some extent the treatment of diabetic gangrene.

COMMENT

There may be deprecated the fact that only four cases out of thousands were chosen to demonstrate this new approach. Although results obtained in many other patients are as dramatic, it is felt that illustrating the system-specific nature of the therapy (from cerebral to leg arteries) would be more effective in demonstrating its efficacy than by the use of a larger number of patients with statistical percentage improvements in the same organ or region.

From the results obtained, there arises the question, "Has the atherosclerotic process been reversed in these cases?" It will be noted that a certain number of "basic" therapeutic agents have been used constantly in a manner which can be repeated by other investigators. These therapeutic agents cover the entire spectrum of known anti-atherosclerogenic agents. The effect on the cholesterol mechanism caused by these agents—a moderately prolonged low level, below what would seem to be the patient's basal cholesterol level—could have created a favorable physiological situation for mobilization of cholesterol from vascular deposits. Whether this is true or not, will be determined by autopsy findings at a later date. It is felt, however,

that the results, even if later found to be of only functional nature, are of sufficient benefit, subjectively and objectively, to make us feel that our method is a positive approach toward the reversal ideal.

SUMMARY AND CONCLUSIONS

1. The thyroid hormone-vitamin B complex therapy of atherosclerosis described seems to counteract the causal disturbances of the oxygen and fat metabolism underlying the continuous or transitory increased lability of the colloiddally dispersed plasma lipoids.
2. The therapy appears to give definite symptomatic improvement of all types of atherosclerosis including advanced forms.
3. Since little hazard to the patient is connected with its discriminate and well-considered use, it is recommended for general application in the control of atherosclerosis.

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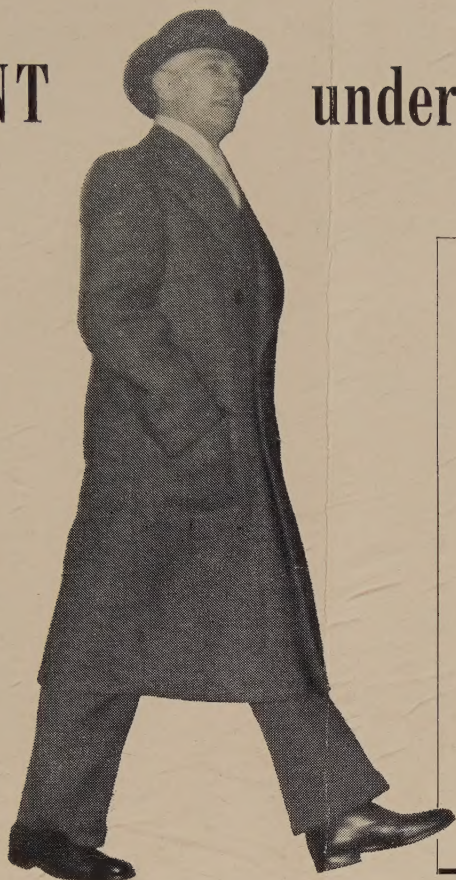
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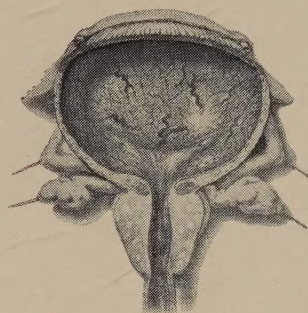
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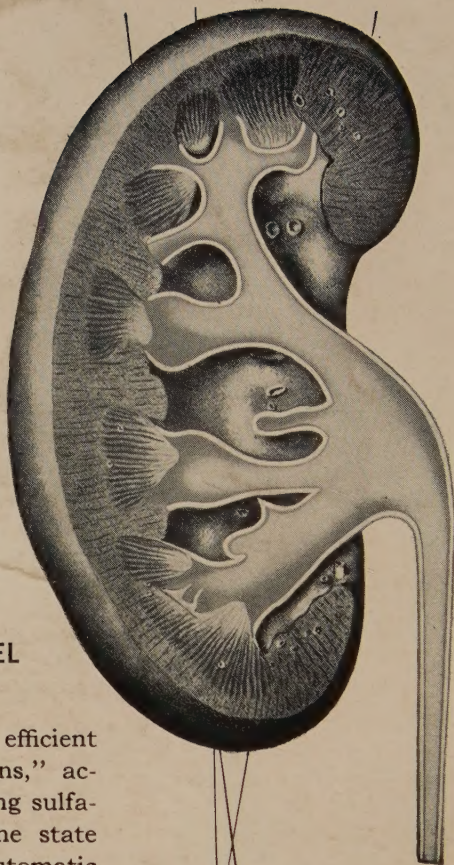


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